
CAELYX[®] INJECTION

Doxorubicin hydrochloride

DATA SHEET

1. PRODUCT NAME

CAELYX[®] 2 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of CAELYX contains 2 mg doxorubicin hydrochloride in a pegylated liposomal formation.

CAELYX, a pegylated liposomal formulation of doxorubicin hydrochloride, contains doxorubicin encapsulated in liposomes having surface-bound methoxypolyethylene glycol groups (pegylated liposomes). This process is known as pegylation and protects the liposomes from detection by the mononuclear phagocyte system (MPS), which increases blood circulation time.

For a full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

CAELYX is a concentrate for infusion presented as a sterile, translucent, red suspension with a pH of 6.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CAELYX is indicated for the treatment of:

- Metastatic breast cancer in women for whom an anthracycline would be considered
- Metastatic breast cancer in women who have failed a taxane-containing regimen
- Advanced epithelial ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.
- AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (<200 lymphocytes/mm³) and extensive mucocutaneous or visceral disease.

CAELYX may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and doxorubicin (or other anthracycline).

CAELYX is also indicated, in combination with bortezomib, for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.

4.2 Dose and method of administration

CAELYX should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents.

CAELYX exhibits unique pharmacokinetic properties and must not be used interchangeably with other formulations of doxorubicin HCl.

Dose

Breast Cancer / Ovarian Cancer:

CAELYX is administered intravenously at a dose of 50 mg/m² once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

For doses <90 mg: dilute CAELYX in 250 ml 5 % (50 mg/mL) glucose solution for infusion.

For doses >90 mg: dilute CAELYX in 500 ml 5 % (50 mg/mL) glucose solution for infusion.

To minimise the risk of infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent CAELYX infusions may be administered over a 60-minute period.

In the breast cancer trial program, modification of the infusion was permitted for those patients experiencing an infusion reaction as follows:

5% of the total dose was infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate was doubled over the next 15 minutes. If tolerated, the infusion was completed over the next hour for a total infusion time of 90 minutes.

Subsequent CAELYX infusions may be administered over a 60 minute period.

Multiple Myeloma:

CAELYX is administered at 30 mg/m² on day 4 of the bortezomib 3 week regimen as a 1 hour infusion administered immediately after the bortezomib infusion. The bortezomib regimen consists of 1.3 mg/m² on days 1, 4, 8, and 11 every 3 weeks. The dose should be repeated as long as patients respond satisfactorily and tolerate treatment.

For doses < 90 mg: dilute CAELYX in 250 ml of 5 % (50 mg/ml) glucose solution for infusion.

For doses ≥ 90 mg: dilute CAELYX in 500 ml of 5 % (50 mg/ml) glucose solution for infusion.

The intravenous catheter and tubing should be flushed with 5 % glucose solution for infusion between administration of CAELYX and bortezomib. Day 4 dosing of both medicinal products may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart. The first infusion of CAELYX should be administered over 90 minutes, as follows:

- 10 ml over first 10 minutes
- 20 ml over next 10 minutes
- 40 ml over next 10 minutes
- then, complete the infusion over a total of 90 minutes.

Subsequent doses of CAELYX will be administered over 1 hour, as tolerated. If an infusion reaction to CAELYX occurs, stop the infusion and after the symptoms resolve, attempt to administer the remaining CAELYX over 90 minutes, as follows:

- 10 ml over first 10 minutes
- 20 ml over next 10 minutes
- 40 ml over next 10 minutes
- then, complete the remaining infusion over a total of 90 minutes.

Infusion may be given through a peripheral vein or a central line.

AIDS Related Kaposi's Sarcoma:

CAELYX should be administered intravenously at 20 mg/m² every two-to-three weeks. Intervals shorter than 10 days should be avoided as drug accumulation and increased toxicity cannot be ruled out. Patients should be treated for two-to-three months to achieve a therapeutic response. Treatment should be continued as needed to maintain a therapeutic response. CAELYX, diluted in 250 mL 5% Glucose Intravenous Infusion, is administered by intravenous infusion over 30 minutes.

All Patients:

If the patient experiences early symptoms or signs of infusion reaction (see **section 4.4**), immediately discontinue the infusion, give appropriate premedications (antihistamine and/or short acting corticosteroid) and restart at a slower rate.

Guidelines for CAELYX Dose Modification:

To manage adverse events such as palmar-plantar erythrodysesthesia (PPE), stomatitis or haematological toxicity, the dose may be reduced or delayed. Guidelines for CAELYX dose modification secondary to these adverse effects are provided in the tables below. The toxicity grading in these tables is based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (US).

The tables for PPE and stomatitis provide the schedule followed for dose modification in clinical trials in the treatment of breast or ovarian cancer (modification of the recommended 4 week treatment cycle). If these toxicities occur in patients with AIDS related KS, the recommended 2 to 3 week treatment cycle can be modified in a similar manner.

The table for hematologic toxicity (**Table 3**) provides the schedule followed for dose modification in clinical trials in the treatment of patients with breast or ovarian cancer only. Dose modification in patients with AIDS-KS is addressed in Adverse Reactions.

Table 1: PALMAR-PLANTAR ERYTHRODYSESTHESIA			
Toxicity Grade at Current Assessment	Week After Prior CAELYX Dose		
	Week 4	Week 5	Week 6
Grade 1 (mild erythema, swelling, or desquamation not interfering with daily activities)	Redose unless Patient has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week	Redose unless patient has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week	Decrease dose by 25%; return to 4 week interval
Grade 2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter)	Wait an additional week	Wait an additional week	Decrease dose by 25%; return to 4 week interval
Grade 3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	Wait an additional week	Wait an additional week	Discontinue CAELYX

Toxicity Grade at Current Assessment	Week After Prior CAELYX Dose		
	Week 4	Week 5	Week 6
Grade 4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalisation)	Wait an additional week	Wait an additional week	Discontinue CAELYX

Table 2: STOMATITIS

Toxicity Grade at Current Assessment	Week After Prior CAELYX Dose		
	Week 4	Week 5	Week 6
Grade 1 (painless ulcers, erythema, or mild soreness)	Redose unless Patient has experienced a previous Grade 3 or 4 stomatitis in which case wait an additional week	Redose unless Patient has experienced a previous Grade 3 or 4 stomatitis in which case wait an additional week	Decrease dose by 25%; return to 4 week interval Or withdraw patient per physician's assessment
Grade 2 (painful erythema, oedema, or ulcers, but can eat)	Wait an additional week	Wait an additional week	Decrease dose by 25%; return to 4 week interval Or withdraw patient per physician's assessment
Grade 3 (painful erythema, oedema, or ulcers, but cannot eat)	Wait an additional week	Wait an additional week	Discontinue CAELYX
Grade 4 (requires parenteral or enteral support)	Wait an additional week	Wait an additional week	Discontinue CAELYX

Table 3: HAEMATOLOGICAL TOXICITY (ANC OR PLATELETS):

1. MANAGEMENT OF PATIENTS WITH BREAST OR OVARIAN CANCER

GRADE	ANC (x10 ⁹ /L)	PLATELETS (x10 ⁹ /L)	MODIFICATION
Grade 1	1.5 - 1.9	75 - 150	Resume treatment with no dose reduction
Grade 2	1.0 - <1.5	50 - <75	Wait until ANC ≥1.5 x 10 ⁹ /L and platelets ≥75 x10 ⁹ /L; redose with no dose reduction
Grade 3	0.5 - <1.0	25- <50	Wait until ANC ≥1.5 x10 ⁹ /L and platelets ≥75 x10 ⁹ /L; redose with no dose reduction
Grade 4	<0.5	<25	Wait until ANC ≥1.5 x10 ⁹ /L and platelets ≥75 x10 ⁹ /L; decrease dose by 25% or continue full dose with growth factor support.

2. MANAGEMENT OF PATIENTS WITH AIDS-KS

GRADE	ANC (x10 ⁹ /L)	PLATELETS (x10 ⁹ /L)	MODIFICATION
Grade 1	1.5 - 1.9	75 - 150	Resume treatment with no dose reduction

GRADE	ANC (x10 ⁹ /L)	PLATELETS (x10 ⁹ /L)	MODIFICATION
Grade 2	1.0 - <1.5	50 - <75	
Grade 3	0.5 - <1.0	25- <50	Wait until ANC ≥1.0 x10 ⁹ /L and platelets ≥50 x10 ⁹ /L; redose with no dose reduction. G-CSF (or GM-CSF) may be given as concomitant therapy to support the blood count when the ANC count is <1 x 10 ⁹ /L.
Grade 4	<0.5	<25	

For multiple myeloma patients treated with CAELYX in combination with bortezomib who experience PPE or stomatitis, the CAELYX dose should be modified as described in **Table 1** and **Table 2** above, respectively. For more detailed information on bortezomib dosing and dosage adjustments, see the Prescribing Information for bortezomib.

Table 4. DOSAGE ADJUSTMENTS FOR CAELYX + BORTEZOMIB COMBINATION THERAPY - PATIENTS WITH MULTIPLE MYELOMA

Patient Status	CAELYX	Bortezomib
Fever ≥ 38°C and ANC < 1,000/mm ³	Do not dose this cycle if before Day 4; if after Day 4, reduce next dose by 25 %.	Reduce next dose by 25 %
On any day of medicine administration after Day 1 of each cycle: Platelet count < 25,000/mm ³ Haemoglobin < 8g/dL ANC < 500/mm ³	Do not dose this cycle if before Day 4; if after Day 4 reduce next dose by 25 % in the following cycles if bortezomib is reduced for haematologic toxicity.*	Do not dose; if 2 or more doses are not given in a cycle, reduce dose by 25 % in following cycles.
Grade 3 or 4 non-haematologic medicine related toxicity	Do not dose until recovered to Grade < 2 and reduce dose by 25 % for all subsequent doses.	Do not dose until recovered to Grade < 2 and reduce dose by 25 % for all subsequent doses.
Neuropathic pain or peripheral neuropathy	No dosage adjustments.	See the PI for bortezomib

*for more information on bortezomib dosing and dosage adjustment, see the PI for bortezomib

Special Populations

Patients with impaired hepatic function:

Prior to CAELYX administration, hepatic function should be evaluated using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase and bilirubin. In a small number of patients with impaired hepatic function (bilirubin values up to 70 micromoles/L) administered 20 mg/m² of CAELYX, there appeared to be no change in the clearance and terminal half-life of CAELYX. However, until further experience is gained, the CAELYX dosage should be reduced in patients with impaired hepatic function, based on experience from the breast and ovarian clinical trial programs as follows:

At initiation of therapy, if the bilirubin is between 20 – 51 micromoles/L, the first dose is reduced by 25%. If the bilirubin is > 51 micromoles/L, the first dose is reduced by 50%. If the patient tolerates the first dose without an increase in serum bilirubin or liver enzymes, the dose for cycle 2 can be increased to the next dose level, i.e., if reduced by 25% for the first dose, increase to full dose for cycle 2; if reduced by 50% for the first dose, increase to 75% of full dose for cycle 2. The dosage can be increased to full dose for subsequent cycles if tolerated. CAELYX can be administered to patients with liver metastases with concurrent elevation of

bilirubin and liver enzymes up to 4 x the upper limit of the normal range. No data are available for patients with severe hepatic impairment.

Patients with impaired renal function:

As doxorubicin is metabolised by the liver and excreted in the bile, dose modification should not be required with CAELYX. Population-based analysis confirms that changes in renal function over the range tested (estimated creatinine clearance 30-156 mL/min) do not alter the pharmacokinetics of CAELYX. No pharmacokinetic data are available in patients with creatinine clearance of less than 30 mL/min.

AIDS-KS patients with splenectomy:

As there is no experience with CAELYX in patients with splenectomy, treatment with CAELYX is not recommended.

Paediatric patients:

The safety and effectiveness in patients less than 18 years of age have not been established.

Elderly patients:

Population based analysis demonstrates that age across the range tested (21–75 years) does not significantly alter the pharmacokinetics of CAELYX.

Method of administration

Caelyx is administered as an intravenous infusion.

CAELYX MUST NOT BE GIVEN BY THE INTRAMUSCULAR OR SUBCUTANEOUS ROUTE (see **section 6.6**).

DO NOT administer as a bolus injection or undiluted solution.

It is recommended that the CAELYX infusion line be connected through the side port of an intravenous infusion of 5% Glucose Intravenous Infusion to achieve further dilution and minimise the risk of thrombosis and extravasation. The infusion may be given through a peripheral vein. Do not use with in-line filters.

For further instructions on preparation and special precautions for handling see **section 6.6**.

4.3 Contraindications

- CAELYX is contraindicated in patients who have a history of hypersensitivity reactions to its components or to doxorubicin HCl.
- CAELYX should not be administered during pregnancy or while breast feeding.
- CAELYX should not be used to treat AIDS-KS that may be effectively treated with local therapy or systemic alfa-interferon.

4.4 Special warnings and precautions for use

For common adverse events which required dose modification or discontinuation see **section 4.8**.

Cardiac Risk

Experience with CAELYX at high cumulative doses is too limited to have established its effects on the myocardium (see **section 4.8**). Moreover, the long-term cardiac effects of CAELYX relative to the conventional formulation of doxorubicin HCl have not been adequately evaluated. Until further clinical data are available, the risk of developing cardiomyopathy is assumed to be similar to that of standard doxorubicin.

All patients receiving CAELYX should routinely undergo frequent ECG monitoring.

Transient ECG changes such as T-wave flattening, S-T segment depression and benign arrhythmias, are not considered mandatory indications for the suspension of CAELYX therapy. However reduction of the QRS complex is considered more indicative of cardiac toxicity. If this change occurs, the most definitive test for anthracycline myocardial injury, i.e. endomyocardial biopsy, should be considered.

More specific methods for evaluation and monitoring of cardiac functions as compared to ECG are a measurement of left ventricular ejection fraction by echocardiography or preferably by multiple gated angiography (MUGA). These methods should be applied routinely before the initiation of CAELYX and should be repeated periodically during treatment. In a phase-III clinical trial comparing CAELYX (50 mg/m² every 4 weeks) versus doxorubicin (60 mg/m² every 3 weeks), the risk of developing a cardiac event as a function of cumulative anthracycline dose was significantly lower with CAELYX than with doxorubicin (HR=3.16, p<0.001). At cumulative doses between 450 mg/m² and 600 mg/m² there was no increased risk of cardiac toxicity with CAELYX. The evaluation of left ventricular function is considered to be mandatory before each additional dose of CAELYX which exceeds a lifetime cumulative dose of anthracyclines (e.g., Adriamycin) of 600 mg/m².

The evaluation tests and methods mentioned above concerning the monitoring of cardiac performance during anthracycline therapy should be employed in the following order, ECG monitoring, measurement of left ventricular ejection fraction, endomyocardial biopsy. If a test result indicates possible cardiac injury associated with CAELYX therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

In patients with cardiac disease requiring treatment, administer CAELYX only when the benefit outweighs the risk to the patient.

Caution should be exercised in patients with impaired cardiac function who receive CAELYX. Whenever cardiomyopathy is suspected, i.e., the left ventricular ejection fraction has substantially decreased relative to pre-treatment values and/or left ventricular ejection fraction is lower than a prognostically relevant value (e.g. <45%), endomyocardial biopsy may be considered and the benefit of continued therapy must be carefully evaluated against the risk of developing irreversible cardiac damage.

Congestive heart failure due to cardiomyopathy may occur suddenly, without prior ECG changes and may also be encountered several weeks after discontinuation of therapy.

Caution should be observed in patients who have received other anthracyclines. The total dose of doxorubicin HCl should also take into account any previous (or concomitant) therapy with cardiotoxic compounds such as other anthracyclines/anthraquinones or e.g., 5-Fluorouracil. Cardiac toxicity also may occur at cumulative anthracycline doses lower than 450 mg/m² in patients with prior mediastinal irradiation or in those receiving concurrent cyclophosphamide therapy.

The cardiac safety profile for the dosing schedule recommended for both breast and ovarian cancer (50 mg/m²) is similar to the 20 mg/m² profile in patients with AIDS-KS.

Myelosuppression

Many patients treated with CAELYX have baseline myelosuppression due to such factors as their HIV disease or numerous concomitant or previous medications, or tumours involving bone marrow. In the pivotal trial in patients with ovarian cancer treated at a dose of 50 mg/m², myelosuppression was generally mild to moderate, reversible, and was not associated with episodes of neutropenic infection or sepsis. Moreover, in a controlled clinical trial of CAELYX vs. topotecan, the incidence of treatment related sepsis was substantially less in the CAELYX-treated ovarian cancer patients as compared to the topotecan treatment group. A similar low incidence of myelosuppression was seen in patients with metastatic breast cancer receiving CAELYX in a first-line trial. In contrast to the experience in patients with breast cancer or ovarian cancer, myelosuppression appears to be the dose-limiting adverse event in patients with AIDS-KS (see **section 4.8**). Because of the potential for bone marrow suppression, periodic blood counts should be performed frequently during the course of CAELYX, and at a minimum, prior to each dose of CAELYX.

Persistent myelosuppression, although not seen in patients with breast or ovarian cancer, may result in superinfection or haemorrhage.

In controlled clinical studies in patients with AIDS-KS against a bleomycin/vincristine regimen, opportunistic infections were apparently more frequent during treatment with CAELYX. Patients and doctors must be aware of this higher incidence and take action as appropriate.

Given the difference in pharmacokinetic profiles and dosing schedules, CAELYX should not be used interchangeably with other formulations of doxorubicin hydrochloride.

Combination therapy with CAELYX has been extensively studied in solid tumour populations. CAELYX has been safely co-administered with standard doses of chemotherapeutic agents that are frequently used in the treatment of advanced breast cancer or ovarian cancer, however the efficacy of such combination regimens has not been established.

Infusion-associated Reactions

Serious and sometimes life-threatening infusion reactions, which are characterised by allergic-like or anaphylactoid-like reactions, may occur within minutes of starting the infusion of CAELYX. Symptoms include asthma, flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial oedema, chills, headache, back pain, tightness in the chest and throat and/or hypotension may occur within minutes of starting the infusion of CAELYX. Very rarely, convulsions also have been observed in relation to infusion reactions (see **section 4.8**). Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medications to treat these symptoms (e.g. antihistamines, corticosteroids, adrenaline and anticonvulsants), as well as emergency equipment should be available for immediate use. In most patients treatment can be resumed after all symptoms have resolved, without recurrence. Infusion reactions rarely recur after the first treatment cycle. To minimise the risk of infusion reactions, the initial dose should be administered at a rate no greater than 1 mg/minute (see **section 4.2**).

Palmar-plantar Erythrodysesthesia

Palmar-plantar erythrodysesthesia (PPE) is characterised by painful, red macular and/or papular bullous skin eruptions. In patients experiencing this event, it is generally seen after two or three cycles of treatment. In most patients it clears in one or two weeks, with or without treatment with corticosteroids. Pyridoxine at a dose of 50-150 mg per day has been used for the prophylaxis and treatment of PPE. Other strategies to prevent and treat PPE include keeping hands and feet cool, by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight-fitting). It appears to be dose- and schedule-related and can be reduced by extending the CAELYX dose interval 1-2 weeks or reducing the CAELYX dose (see **section 4.2**). This reaction can be severe and debilitating in some patients, however, and may require discontinuation of treatment.

Extravasation Injury

Although local necrosis following extravasation has been reported very rarely, CAELYX should be considered an irritant. Although animal studies indicate that the administration of doxorubicin HCl as a liposomal formulation reduces the potential for extravasation injury, the possibility of doxorubicin-related skin injury exists, and care should be taken to avoid extravasation of CAELYX. If any signs or symptoms of extravasation occur (e.g. stinging, erythema) the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. CAELYX must not be given by the intramuscular or subcutaneous route.

Recall of skin reaction due to prior radiotherapy has rarely occurred with CAELYX administration.

Diabetic Patients

It should be noted that each vial of CAELYX contains sucrose and is administered in 5% Glucose Intravenous Infusion.

Secondary oral neoplasms

Very rare cases of secondary oral cancer have been reported in patients with long term (more than one year) exposure to CAELYX or those receiving a cumulative CAELYX dose greater than 720 mg/m². Cases of secondary oral cancer were diagnosed both, during treatment with CAELYX, and up to 6 years after the last dose. Patients should be examined at regular intervals for the presence of oral ulceration or any oral discomfort that may be indicative of secondary oral cancer.

4.5 Interactions with other medicines and other forms of interaction

No formal drug interaction studies have been conducted with CAELYX, although phase II combination trials with conventional chemotherapy agents have been conducted in patients with gynaecological malignancies. Caution should be exercised in the concomitant use of drugs known to interact with doxorubicin HCl. Although not formally studied, CAELYX, like other doxorubicin HCl preparations, may potentiate the toxicity of other anti-cancer therapies.

In patients with solid tumours (including breast and ovarian cancer) who received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted. In patients with AIDS-KS, exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with doxorubicin HCl. Caution should be exercised when giving any other cytotoxic agents, especially myelotoxic agents, at the same time.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category D. CAELYX is embryotoxic at doses of 1 mg/kg/day in rats (about 1/3 the recommended human dose on a mg/m² basis). CAELYX is embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (about 1/4 the recommended human dose on a mg/m² basis). Embryotoxicity was characterised by increased embryo-foetal deaths and reduced litter sizes.

There are no adequate and well-controlled studies in pregnant women. If CAELYX is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the foetus and such treatment should only proceed with the patient's complete informed consent.

Women of child-bearing potential

Women of childbearing potential should be advised to avoid pregnancy while they or their male partner are receiving CAELYX and in the six months following discontinuation of CAELYX therapy.

Breastfeeding

It is not known whether this drug is excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CAELYX, mothers should discontinue nursing prior to taking this drug. Health experts recommend that HIV-infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on the ability to drive and use machines

Although CAELYX should not affect driving performance, in studies to date, dizziness and somnolence were associated infrequently (<5%) with the administration of CAELYX. Patients who suffer from these effects should avoid driving and operating machinery.

4.8 Undesirable effects

Breast Cancer Patients (Dosage: 50mg/m²)

254 patients with advanced breast cancer who had not received prior chemotherapy for metastatic disease were treated with CAELYX at a dose of 50 mg/m² every 4 weeks in a phase III clinical trial (I97-328). The most frequently reported treatment related adverse effects included palmar-plantar erythrodysesthesia (PPE) (48.0 %) and nausea (37.0 %) (see **Table 5**). These effects were mostly mild and reversible, with severe (Grade III) cases reported in 17.0 % and 3.0 % respectively, and no reported incidences of life threatening (Grade IV) cases for either PPE or nausea. Infrequently, these effects resulted in permanent treatment discontinuation (7.0 % and 0 % respectively). Pronounced alopecia (or total hair loss) was seen in only 7.0 % of CAELYX-treated patients as compared with 54.0 % of patients treated with doxorubicin.

Haematologic adverse effects were infrequently reported and were mostly mild or moderate in severity and manageable. Anaemia, neutropenia, leucopenia and thrombocytopenia were infrequently reported at incidences of 5.0 %, 4.0 %, 2.0 %, and 1.0 %, respectively. Life threatening (Grade IV) haematologic effects were reported at incidences of < 1.0 %. The need for either growth factor support or transfusion support was minimal (5.1 % and 5.5 % of patients, respectively).

Clinically significant laboratory abnormalities (Grades III and IV) in this breast cancer group included increases in total bilirubin (2.4 %) and AST (1.6 %). Increases in ALT were less frequent (< 1 %). Clinically significant haematologic measurements were infrequent as measured by leucopenia (4.3 %), anaemia (3.9 %), neutropenia (1.6 %) and thrombocytopenia (1.2 %). Sepsis was reported at an incidence of 1 %. No clinically significant increases in serum creatinine were reported.

In 150 patients with advanced breast cancer who had failed a prior first or second line taxane-containing chemotherapy regimen and were subsequently treated with CAELYX at a dose of 50 mg/m² every 4 weeks in a phase III clinical trial (C/I96-352), the safety profile was consistent with that reported for CAELYX in previous studies using the same dosage regimen (see **Table 5**). The proportion of patients experiencing clinically significant laboratory abnormalities was low and comparable numerically to the 254 breast cancer patients receiving CAELYX as first-line therapy, with the exception of leucopenia (20 %).

Table 5. Treatment Related Undesirable Effects Reported in Breast Cancer Clinical Trials (I97-328 and C/I96-352) (≥ 5 % of CAELYX-treated patients) by Severity, Body System and Preferred Term

AE by body system	I97-328 All Severities %	I97-328 Grades III/IV %	C/I96-352 All Severities %	C/I96-352 Grades III/IV %
Autonomic Nervous System				
Flushing	3	< 1	5	< 1
Body as a whole				
Asthenia	10	1	9	1
Erythema	7	< 1	6	2
Fatigue	12	< 1	20	4
Fever	8	0	4	< 1
Weakness	6	< 1	0	0
Weight Decrease	3	< 1	5	0
Gastro-intestinal system				
Abdominal Pain	8	1	4	< 1
Anorexia	11	1	11	0
Constipation	8	< 1	5	0
Diarrhoea	7	1	10	< 1

AE by body system	I97-328	I97-328	C/I96-352	C/I96-352
	All Severities	Grades III/IV	All Severities	Grades III/IV
	%	%	%	%
Dyspepsia	3	0	5	0
Mouth Ulceration	5	< 1	< 1	0
Mucositis Nose	23	4	14	3
Nausea	37	3	31	3
Stomatitis	22	5	21	5
Vomiting	19	< 1	19	4
Red Blood Cell Disorders				
Anaemia	5	1	2	0
Respiratory System				
Dyspnoea	2	1	6	3
Skin and appendages				
Alopecia	20	0	3	0
Dry skin	2	0	5	0
PPE*	48	17	37	19
Pigmentation abnormal	8	< 1	< 1	0
Pruritus	3	< 1	5	0
Rash	10	2	15	2
Skin Discolouration	2	0	5	< 1

* Palmar-plantar erythrodysesthesia (Hand- foot syndrome). One case of Grade IV (life threatening) PPE was reported in C/I96-352, no cases were reported in I97-328.

Adverse effects reported between 1 % and 5 % in 404 CAELYX-treated breast cancer patients, not previously reported in CAELYX clinical trials (≥ 1 %) were breast pain, leg cramps, oedema, leg oedema, peripheral neuropathy, oral pain, ventricular arrhythmia, folliculitis, bone pain, musculo-skeletal pain, thrombocytopenia, cold sores (non-herpetic), fungal infection, epistaxis, upper respiratory tract infection, bullous eruption, dermatitis, erythematous rash, nail disorder, scaly skin, lacrimation, and blurred vision.

A 12.4% incidence of infusion-related adverse events was observed in pivotal breast cancer trials. Permanent treatment discontinuation was reported at 1.5%

In Ovarian Cancer Patients (Dosage 50 mg/m²)

Based on the experience in 512 patients with ovarian cancer treated at a dose of 50 mg/m², the frequency of adverse events reported in clinical trials is listed below and classified according to body systems:

Cardiovascular

Common (>1% and <10%): cardiovascular disorder, vasodilatation, cardiac toxicity (see All Patients)

Uncommon (>0.1% and <1%): palpitation

Dermatological

Very Common (>10%): palmar-plantar erythrodysesthesia (PPE), rash, alopecia

Common (>1% and <10%): skin discolouration, dry skin, pruritus, vesiculobullous rash, skin disorder, exfoliative dermatitis, maculopapular rash, acne, skin ulcer

Uncommon (>0.1% and <1%): PPE (Grade IV - life threatening), nail disorder

The overall incidence of PPE was very common at 46.1%. This comprised, in decreasing order of frequency, Grade III (severe) 19.5%, Grade II (Moderate) 16.4%, Grade I (Mild) 9.6%, and Grade IV (life threatening) 0.6%.

Gastrointestinal

Very Common (>10%): stomatitis, nausea, vomiting, constipation, diarrhoea, anorexia

Common (>1% and <10%): stomatitis (Grade III - severe), abdominal pain, dyspepsia, weight loss, oesophagitis, gastritis, dysphagia, mouth ulceration, nausea and vomiting, oral moniliasis, gingivitis, flatulence, dry mouth, hyperbilirubinemia (usually in patients with liver metastases)

Uncommon (>0.1% and <1%): stomatitis (Grade IV - life threatening), increased AST

Haematological

Very Common (\geq 10%): anaemia (32.2%), leucopenia (33.2%), neutropenia (31.6%), thrombocytopenia (10.7%)

Common (\geq 1% and <10%): neutropenia (Grade IV - life threatening) (2.9%), leucopenia (Grade IV - life threatening) (1.6%), hypochromic anaemia

Uncommon (>0.1% and <1%): anaemia (Grade IV - life threatening) (0.4%), thrombocytopenia (Grade IV - life threatening) (0.2%), sepsis related to leucopenia

In the 512 patients with ovarian cancer treated at a dose of 50 mg/m², myelosuppression was mostly mild or moderate and manageable. Growth factor was required infrequently (<5%) and transfusion support was required in approximately 15% of the patients (see **section 4.2**).

Musculoskeletal

Common (>1% and <10%): myalgia

Neurological

Common (>1% and <10%): paraesthesia, somnolence, dizziness, depression, insomnia, anxiety, neuropathy

Uncommon (>0.1% and <1%): peripheral neuritis

Ocular

Common (>1% and <10%): conjunctivitis

Uncommon (>0.1% and <1%): amblyopia

Respiratory

Common (>1% and <10%): dyspnoea, increased cough, pharyngitis,

Uncommon (>0.1% and <1%): rhinitis

Urogenital

Common (>1% and <10%): urinary tract infection, dysuria, vaginitis, increased serum creatinine

General

Very Common (>10%): asthenia, mucous membrane disorder, Infusion reactions

Common (>1% and <10%): fever, pain, headache, peripheral oedema, allergic reaction, dehydration, chills, infection, chest pain, back pain, malaise, sweating, taste perversion, herpes zoster, cachexia, hypertonia

Uncommon (>0.1% and <1%): enlarged abdomen, facial oedema

In Multiple Myeloma Patients (Dosage: 30 mg/m²):

Of 646 patients with multiple myeloma who have received at least 1 prior therapy, 318 patients were treated with combination therapy of CAELYX 30 mg/m² as a one hour intravenous infusion administered on day 4 following bortezomib which is administered at 1.3 mg/m² on days 1, 4, 8, and 11, every three weeks or with bortezomib monotherapy in a phase III clinical trial. See Table 5 for adverse effects reported in ≥ 5 % patients treated with combination therapy of CAELYX plus bortezomib.

Neutropaenia, thrombocytopaenia, and anaemia were the most frequently reported haematologic events reported with both combination therapy of CAELYX plus bortezomib and bortezomib monotherapy. The incidence of grade 3 and 4 neutropaenia was higher in the combination therapy group than in the monotherapy group (28 % vs. 14 %). The incidence of grade 3 and 4 thrombocytopaenia was higher in the combination therapy group than in the monotherapy group (22 % vs. 14 %). The incidence of anaemia was similar in both treatment groups (7 % vs. 5 %).

Nausea and vomiting were reported more frequently in the combination therapy group (40 % and 28 %) than in the monotherapy group (32 % and 15 %) and were mostly grade 1 and 2 in severity.

Stomatitis was reported more frequently in the combination therapy group (16 %) than in the monotherapy group (3 %), and most cases were grade 2 or less in severity. Grade 3 stomatitis was reported in 2 % of patients in the combination therapy group. No grade 4 stomatitis was reported.

Treatment discontinuation of one or both agents due to adverse events was seen in 38 % of patients. Common adverse events which led to treatment discontinuation of bortezomib and CAELYX included PPE, neuralgia, peripheral neuropathy, peripheral sensory neuropathy, thrombocytopaenia, decreased ejection fraction, and fatigue.

The most frequently reported treatment-emergent medicine-related adverse events (**Table 6**) in combination therapy were nausea (40 %), diarrhoea (35 %), neutropaenia (33 %), thrombocytopaenia (29 %), vomiting (28 %), fatigue (27 %), and constipation (22 %). PPE was reported in 16% of multiple myeloma patients treated with combination therapy. Grade 3 PPE was reported in 5% of patients. No grade 4 PPE was reported.

Table 6 Treatment Related Undesirable Effects Reported in Multiple Myeloma MMY-3001 Clinical Trial (Caelyx 30 mg/m² I.V. on day 4 in combination with bortezomib) (≥ 1 % of CAELYX-treated patients) by Severity, MedDRA System Organ Class and Preferred Term

AE by body system	GRADE III %	GRADE IV %	ALL %
Infections and infestations			
Herpes simplex	-	-	8
Herpes zoster	1	-	6
Nasopharyngitis	-	-	3
Oral candidiasis	-	-	1
Pneumonia	2	< 1	3
Upper respiratory tract infection	<1	-	4
Blood and lymphatic system disorders			
Anaemia	6	1	18
Febrile neutropenia	2	< 1	3
Leucopenia	3	2	8
Lymphopenia	< 1	< 1	2
Neutropaenia	20	8	33
Thrombocytopaenia	11	11	29
Metabolism and Nutrition disorders			
Anorexia	1	-	16
Decreased appetite	< 1	-	8

AE by body system	GRADE III	GRADE IV	ALL
	%	%	%
Dehydration	< 1	-	3
Hyperkalaemia	< 1	-	2
Hypocalcaemia	-	< 1	1
Hypokalaemia	1	< 1	3
Hypomagnesaemia	-	-	2
Hyponatraemia	< 1	< 1	1
Psychiatric disorders			
Insomnia	-	-	5
Anxiety	< 1	-	2
Nervous system disorders			
Dizziness	1	-	6
Dysaesthesia	-	-	1
Dysgeusia	-	-	5
Headache	< 1	< 1	10
Hypoaesthesia	-	-	2
Lethargy	< 1	-	3
Neuralgia	3	-	14
Neuropathy	1	-	8
Paraesthesia	< 1	-	9
Peripheral neuropathy	2	-	9
Peripheral sensory neuropathy	< 1	-	10
Polyneuropathy	-	-	6
Syncope	< 1	-	1
Eye disorders			
Conjunctivitis	-	-	3
Vascular disorders			
Flushing	-	-	2
Hypertension	< 1	-	1
Hypotension	1	-	4
Orthostatic hypotension	< 1	-	3
Phlebitis	-	-	1
Respiratory, thoracic, and mediastinal disorders			
Cough	-	-	6
Dyspnoea	< 1	-	5
Epistaxis	< 1	-	2
Exertional dyspnoea	< 1	-	2
Gastrointestinal disorders			
Abdominal pain	< 1	-	7
Aphthous stomatitis	-	-	1
Constipation	< 1	-	22
Diarrhoea	7	-	35
Dry mouth	-	-	2
Dyspepsia	< 1	-	5
Dysphagia	< 1	-	2
Mouth ulceration	-	-	1
Nausea	2	-	40
Stomatitis	2	-	16
Upper abdominal pain	< 1	-	4
Vomiting	4	-	28
Skin and subcutaneous tissue disorders			
Allergic dermatitis	-	-	1
Alopecia	-	-	2
Drug Eruption	-	-	2
Dry skin	-	-	5
Erythema	-	-	3
Papular rash	-	-	3
Petechiae	-	-	2

AE by body system	GRADE III	GRADE IV	ALL
	%	%	%
PPE*	5	-	16
Pruritus	< 1	-	3
Rash	< 1	-	11
Skin hyperpigmentation	-	-	3
Musculoskeletal and connective tissue disorders			
Arthralgia	< 1	-	4
Muscle spasms	-	-	2
Muscular weakness	-	-	2
Musculoskeletal chest pain	-	-	1
Musculoskeletal pain	-	-	1
Myalgia	-	-	3
Pain in extremity	-	-	5
Reproductive system and breast disorders			
Scrotal erythema	< 1	-	1
General disorders and administration site conditions			
Asthenia	5	-	16
Chills	-	-	4
Fatigue	5	< 1	27
Hyperthermia	< 1	-	2
Influenza like illness	< 1	-	3
Malaise	-	-	3
Peripheral oedema	-	-	4
Pyrexia	< 1	-	18
Investigations			
Alanine aminotransferase increased	-	-	1
Aspartate aminotransferase increased	-	-	3
Blood creatinine increased	-	-	2
Ejection fraction decreased	-	-	3
Weight decreased	-	-	8

* Palmar-plantar erythrodysesthesia (Hand-foot syndrome)

In AIDS-KS Patients (Dosage: 20 mg/m²)

CAELYX has been evaluated for safety in 825 AIDS-KS patients treated in 5 clinical trials. Myelosuppression was the most prevalent side effect considered related to CAELYX treatment occurring in approximately half of the patients.

Cardiovascular

Uncommon ($\geq 0.1\%$ and $< 1\%$): congestive heart failure, cardiomyopathy and cardiotoxicity (see All Patients)

Gastrointestinal

Very common ($\geq 10\%$): nausea

Common ($\geq 1\%$ and $< 10\%$): abdominal pain, anorexia, constipation, diarrhoea, glossitis, mouth ulceration, oral moniliasis, nausea and vomiting, vomiting, weight loss, stomatitis, increased alkaline phosphatase, increased AST and hyperbilirubinemia (believed to be disease-related)

Haematological

Very common ($\geq 10\%$): leucopenia, anaemia

Common ($\geq 1\%$ and $< 10\%$): thrombocytopenia, laboratory abnormalities

Uncommon ($\geq 0.1\%$ and $< 1\%$): sepsis related to leucopenia

Leucopenia is the most common adverse event experienced with CAELYX in this population; and can occur during all cycles of administration of CAELYX. In clinical trials, patients rarely discontinued treatment due to myelosuppression. Haematological toxicity may require dose reduction or suspension or delay of therapy (see **section 4.2**). The haematological toxicity for ovarian cancer patients is less severe than in the AIDS-KS setting (see section for **ovarian cancer patients** above).

Dermatological

Common ($\geq 1\%$ and $< 10\%$): alopecia, palmar-plantar erythrodysesthesia, rash.

Rare ($\geq 0.01\%$ and $< 0.1\%$): recall of skin reaction due to prior radiotherapy has rarely occurred with CAELYX administration.

Respiratory

Very common ($\geq 10\%$): opportunistic infections (may be related to HIV-induced immunodeficiency). The most frequently observed OI's in clinical studies were candidiasis, cytomegalovirus, herpes simplex, Pneumocystis carinii pneumonia and Mycobacterium avium complex.

Common ($\geq 1\%$ and $< 10\%$): dyspnoea

Ocular

Common ($\geq 1\%$ and $< 10\%$): retinitis

General

Very Common ($\geq 10\%$): asthenia

Common ($\geq 1\%$ and $< 10\%$): allergic reaction, fever, paraesthesia, vasodilatation, infusion-associated reactions characterised by flushing, shortness of breath, facial oedema, headache, chills, back pain, tightness in the chest and throat and/or hypotension.

Uncommon ($\geq 0.1\%$ and $< 1\%$): anaphylactoid reactions, convulsion, tumour necrosis.

All Patients

100 out of 929 patients (10.8 %) with solid tumours were described as having an infusion-associated reaction during treatment with CAELYX as defined by the following Costart terms: allergic reaction, anaphylactoid reaction, asthma, face oedema, hypotension, vasodilatation, urticaria, back pain, chest pain, chills, fever, hypertension, tachycardia, dyspepsia, nausea, dizziness, dyspnoea, pharyngitis, rash, pruritus, sweating, injection site reaction and drug interaction. Permanent treatment discontinuation rates were infrequently reported at 2 %. Very rarely, convulsions have been observed in relation to infusion reactions. In patients with multiple myeloma receiving CAELYX plus bortezomib, infusion-associated reactions have been reported at a rate of 3%. In all patients, infusion-associated reactions occurred primarily during the first infusion (see **section 4.4**).

Myelosuppression associated with anaemia, thrombocytopenia, leucopenia, and rarely febrile neutropenia, has been reported in CAELYX-treated patients.

Endomyocardial biopsies on nine of ten AIDS-KS patients receiving cumulative doses of CAELYX greater than 460 mg/m², indicate no evidence of anthracycline-induced cardiomyopathy. However, until further clinical data are available, the risk of developing

cardiomyopathy is assumed to be similar to that of standard doxorubicin. The recommended dose of CAELYX for AIDS-KS patients is 20 mg/m² every two-to-three weeks. The cumulative dose at which cardiotoxicity would become a concern (>400 mg/m²) would require more than 20 courses of CAELYX therapy over 40 to 60 weeks.

In addition, endomyocardial biopsies were performed in 8 solid tumour patients (including patients with ovarian or breast cancer) with cumulative anthracycline doses of 509 mg/m²– 1,680 mg/m². The range of Billingham cardiotoxicity scores was grades 0 - 1.5. These grading scores are consistent with no or mild cardiac toxicity.

In the pivotal phase III trial versus doxorubicin, 10/254 patients randomized to receive CAELYX (treated at a dose of 50mg/m² every 4 weeks) versus 48/255 patients randomised to receive doxorubicin (treated at a dose of 60 mg/m²/every 3 weeks) met the protocol-defined criteria for cardiac toxicity during treatment and/or follow-up. Cardiac toxicity was defined as a decrease of 20 points or greater from baseline if the resting LVEF remained in the normal range or a decrease of 10 points or greater if the LVEF became abnormal (less than the lower limit for normal). Patients were also assessed for signs and symptoms of congestive heart failure (CHF). None of the 10 CAELYX patients who had cardiac toxicity by LVEF criteria developed signs and symptoms of CHF. In contrast, 10 of 48 doxorubicin patients who had cardiac toxicity by LVEF criteria also developed signs and symptoms of CHF.

In patients with solid tumours, including a subset of patients with breast and ovarian cancers, treated at a dose of 50 mg/m²/cycle with lifetime cumulative anthracycline doses up to 1,532 mg/m², the incidence of clinically significant cardiac dysfunction was low. Of the 929 patients treated with CAELYX 50 mg/m²/cycle, baseline measurement of left ventricular ejection fraction (LVEF) and at least one follow-up measurement were conducted in 418 patients and assessed by MUGA scan. Of these 418 patients, 88 patients had a cumulative anthracycline dose of > 400 mg/m², an exposure level associated with an increased risk of cardiovascular toxicity with the conventional formulation of doxorubicin. Only 13 of these 88 patients (15 %) had at least one clinically significant change in their LVEF, defined as an LVEF value less than 45 % or a decrease of at least 20 points from baseline. Furthermore, only 1 patient (who received a cumulative dose of 944 mg/m²), discontinued study treatment because of clinical symptoms of congestive heart failure.

Following the marketing of CAELYX, serious skin conditions including erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis have been reported very rarely.

Patients with cancer are at increased risk for thromboembolic disease. In patients treated with CAELYX, cases of thrombophlebitis and venous thrombosis are seen uncommonly, as well as rare cases of pulmonary embolism.

Secondary oral neoplasms

Very rare cases of secondary oral cancer have been reported in patients with long term (more than one year) exposure to CAELYX or those receiving a cumulative CAELYX dose greater than 720 mg/m² (see **section 4.4**).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Acute overdosage with doxorubicin HCl worsens the toxic effects of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage of the severely myelosuppressed patient consists of hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances), ATC code: L01DB01.

The active ingredient of CAELYX is doxorubicin HCl, a cytotoxic anthracycline antibiotic. The exact mechanism of the antitumour activity of doxorubicin is not known. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effect. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix, thus preventing their unwinding for replication.

Clinical Studies

Breast Cancer

A phase III randomized study of CAELYX versus doxorubicin hydrochloride in patients with metastatic breast cancer was completed in 509 patients. The protocol-specified objective of demonstrating non-inferiority between CAELYX and doxorubicin was met, the hazard ratio (HR) for progression-free survival (PFS) was 1.00 (95 % CI for HR=0.82 - 1.22). The treatment HR for PFS when adjusted for prognostic variables was consistent with PFS for the ITT population.

301 patients with advanced breast cancer who had failed a taxane-containing regimen were randomized in a phase III comparative study to CAELYX versus an approved salvage regimen (vinorelbine or mitomycin C + vinblastine). Progression-free survival (PFS) was similar for CAELYX and the active comparator, with a strong trend favouring CAELYX (HR=1.26, 95% CI 0.98 - 1.62, p=0.11). In all subgroups analyzed, including those patients ≥ 55 years of age (n=166), there was a consistent treatment effect with PFS favouring CAELYX over the active comparator (all hazard ratios were > 1.00).

Ovarian Cancer

A Phase III comparative study of CAELYX (50mg/m² every 4 weeks) versus topotecan (1.5 mg/m² for 5 days every 3 weeks) in patients with epithelial ovarian cancer following failure of first-line, platinum based chemotherapy was completed in 474 patients. There was a benefit in overall survival (OS) for CAELYX-treated patients over topotecan-treated patients as indicated by a hazard ratio (HR) of 1.216 (95% CI; 1.000, 1.478), p=0.050. The survival rates at 1, 2 and 3 years were 56.3%, 34.7% and 20.2% respectively on CAELYX, compared to 54.0%, 23.6% and 13.2% on topotecan.

For the sub-group of patients with platinum sensitive disease the difference was greater: HR of 1.432 (95% CI; 1.066, 1.923), p=0.017. The survival rates at 1, 2 and 3 years were 74.1%, 51.2% and 28.4% respectively on CAELYX, compared to 66.2%, 31.0% and 17.5% on topotecan.

The treatments were similar in the sub-group of patients with platinum refractory disease: HR of 1.069 (95% CI; 0.823, 1.387), p=0.618. The survival rates at 1, 2 and 3 years were 41.5%, 21.1% and 13.8% respectively on CAELYX, compared to 43.2%, 17.2% and 9.5% on topotecan.

Multiple Myeloma

A phase III randomised, parallel-group, open-label, multicentre study comparing the safety and efficacy of CAELYX plus bortezomib combination therapy with bortezomib monotherapy in patients with multiple myeloma who have received at least 1 prior therapy was conducted in 646 patients. There was a significant improvement in the primary endpoint of time to progression (TTP) for patients treated with combination therapy of CAELYX plus bortezomib compared to patients treated with bortezomib monotherapy as indicated by a risk reduction (RR) of 35 % (95 % CI; 21-47 %), p<0.0001, based on 407 TTP events. The median TTP was 6.9 months for the bortezomib monotherapy patients compared with 8.9 months for the

CAELYX plus bortezomib combination therapy patients. A protocol-defined interim analysis (based on 249 TTP events) triggered early study termination for efficacy. This interim analysis showed a TTP risk reduction of 45 % (95 % CI; 29-57 %), $p < 0.0001$. The median TTP was 6.5 months for the bortezomib monotherapy patients compared with 9.3 months for the CAELYX plus bortezomib combination therapy patients. These results, though not mature, constituted the protocol defined final analysis.

AIDS-KS

Five clinical studies in patients with AIDS-KS were evaluated. The primary study was conducted in 258 patients and was an open, randomised comparative study comparing the efficacy and safety of CAELYX (133 patients) versus Adriamycin, bleomycin and vincristine (ABV, 125 patients). The other studies, which provide supportive data, were open, non-randomised studies of the use of CAELYX for the treatment of AIDS-related KS.

In the primary study, CAELYX was administered at a dose of 20 mg/m² by intravenous infusion every 2 weeks. The doses of ABV were Adriamycin 20 mg/m², bleomycin 10 U/m² and vincristine 1.0 mg every 2 weeks. Both treatment arms were to continue for a maximum of 6 cycles of treatment. The two groups were well matched for age, sex, weight, prior chemotherapy, HIV risk factor, immune status and severity of KS. All patients were assessed for tumour burden, immune competence and systemic illness factors using the AIDS Clinical Trials Group criteria for staging KS. In each arm, 31% of patients were poor risk for all three criteria. The median CD4+ cell count was 12.5 cells/mm³ in the CAELYX arm and 13 cells/mm³ in the ABV arm. The majority of patients had 25 or more lesions (74.6% in the CAELYX group and 69.7% in the ABV group).

Most patients in each arm were taking a variety of medication. In the CAELYX arm, 52.6% of patients were taking anti-retroviral drugs compared with 63.2% in the ABV arm. More than half the patients (56.4% CAELYX and 57.6% ABV) were taking acyclovir, 64.7% of CAELYX patients were taking co-trimoxazole compared with 64.0% of ABV patients and fluconazole was used in 72.2% of CAELYX patients and 71.2% of patients receiving ABV.

Overall there were significantly more responders in the patients randomised to CAELYX. The response rate for those receiving CAELYX was 46% compared with 26% for those receiving ABV ($p < 0.001$). The median time to CR or PR was 38 days for CAELYX and 50 days for ABV ($p = 0.014$) where the time to response was recorded as the time the best response occurred relative to the time of beginning treatment. Once response occurred, the duration of response was very similar in each group, the median duration of response was 90 days for the CAELYX group compared with 92 days for ABV ($p = 0.234$). The response rate at the end of treatment was 36.1% for the CAELYX group and 21.5% for those receiving ABV ($p = 0.023$). Two-thirds of the patients randomised to CAELYX completed 6 cycles of treatment and one-third of those randomised to ABV completed the protocol. This corresponded to a total number of doses of 692 in the CAELYX group and 479 in the ABV group. Of those patients who discontinued early, adverse events were the cause of discontinuation for 14 patients in the CAELYX arm and 46 in the ABV arm.

With respect to the efficacy of CAELYX in patients who have failed prior chemotherapy, a retrospective analysis was conducted in refractory patients enrolled into one of the non-randomised studies. For the best conservative response (best response maintained for at least 3 weeks) in the 77 patients in this group, the response rate by the investigator assessment was 44%. The response was reached in a mean time of 128 days and continued for 118 days. In forty-nine of these patients who had received prior doxorubicin, the response rate by investigator assessment was 44.9%, and in 43 patients who had disease progression on prior doxorubicin the response rate was 39.5%.

5.2 Pharmacokinetic properties

CAELYX is a long-circulating pegylated liposomal formulation of doxorubicin HCl that provides greater concentration of doxorubicin in Kaposi's sarcoma (KS) tumours than in normal skin. Pegylated liposomes contain surface-grafted segments of the hydrophilic polymer methoxypolyethylene glycol (MPEG). These linear MPEG groups extend from the liposome surface creating a protective coating that reduces interactions between the lipid bilayer membrane and the plasma components. This allows the CAELYX liposomes to circulate for prolonged periods in the blood stream. Pegylated liposomes are small enough (average diameter of approximately 100 nm) to pass intact (extravasate) through defective blood vessels supplying tumours. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumours has been seen in mice with C-26 colon carcinoma tumours and in transgenic mice with KS-like lesions. The pegylated liposomes also have a low permeability lipid matrix and internal aqueous buffer system that combine to keep doxorubicin HCl encapsulated during liposome residence time in circulation.

The plasma pharmacokinetics of CAELYX in humans differs significantly from those reported in the literature for standard doxorubicin HCl preparations. At lower doses (10 mg/m² – 20 mg/m²) CAELYX displayed linear pharmacokinetics. Over the dose range of 10 mg/m² – 60 mg/m² CAELYX displayed non-linear pharmacokinetics. Standard doxorubicin HCl displays extensive tissue distribution (volume of distribution, 700 to 1,100 L/m²) and a rapid elimination clearance (24 to 73 L/h/m²). In contrast, the pharmacokinetic profile of CAELYX indicates that CAELYX is confined mainly to the vascular fluid volume and that the clearance of doxorubicin from the blood is dependent upon the liposomal carrier. Doxorubicin becomes available after the liposomes are extravasated and enter the tissue compartment.

At equivalent doses, the plasma concentration and AUC values of CAELYX which represent mostly pegylated liposomal doxorubicin HCl (containing 90% to 95% of the measured doxorubicin) are significantly higher than those achieved with standard doxorubicin HCl preparations.

Population Pharmacokinetics

The pharmacokinetics of CAELYX were evaluated in 120 patients from 10 different clinical trials using the population pharmacokinetic approach. The pharmacokinetics of CAELYX over the dose range of 10 mg/m² to 60 mg/m² was best described by a two compartment non-linear model with zero order input and Michaelis-Menten elimination. The mean intrinsic clearance of CAELYX was 0.030 L/h/m² (range 0.008 to 0.152 L/h/m²) and the mean volume of distribution at steady state was 2.43 L/m² (range 1.10 – 4.85 L/m²). The apparent half-life ranged from 24 – 231 hours, with a mean of 73.9 hours.

There were no data for patients with severe renal or hepatic impairment.

Breast Cancer Patients

The pharmacokinetics of CAELYX determined in 18 patients with breast carcinoma were similar to the pharmacokinetics determined in the larger population of 120 patients with various cancers. The mean intrinsic clearance was 0.016 l/h/m² (range 0.009 - 0.027 l/h/m²), the mean central volume of distribution was 1.46 l/m² (range 1.10 - 1.64 l/m²). The mean apparent half-life was 71.5 hours (range 45.2 - 98.5 hours).

Ovarian Cancer Patients

The pharmacokinetics of CAELYX determined in 11 patients with ovarian carcinoma were similar to the pharmacokinetics determined in the larger population of 120 patients with various cancers. The mean intrinsic clearance was 0.021 L/h/m² (range 0.009 – 0.041 L/h/m²), the mean volume of distribution at steady state was 1.95 L/m² (range 1.67 – 2.40 L/m²). The mean apparent half-life was 75.0 hours (range 36.1 – 125 hours).

AIDS-KS Patients

The plasma pharmacokinetics of CAELYX were evaluated in 23 patients with Kaposi's sarcoma who received single doses of 20 mg/m² administered by a 30-minute infusion. The pharmacokinetic parameters of CAELYX (primarily representing liposome-encapsulated doxorubicin and low levels of unencapsulated doxorubicin HCl) observed after the 20 mg/m² doses are presented in the following table.

Pharmacokinetic Parameters in CAELYX-Treated AIDS-KS Patients

Parameter	Mean ± Standard error
	20 mg/m ² n = 23
Maximum Plasma Concentration ^a (µg/mL)	8.34 ± 0.49
Plasma Clearance (L/h/m ²)	0.041 ± 0.004
Volume of Distribution (L/m ²)	2.72 ± 0.120
AUC (µg/mL·h)	590 ± 58.7
λ ₁ half-life (hours)	5.2 ± 1.4
λ ₂ half-life (hours)	55.0 ± 4.8

^a Measured at the end of a 30-minutes infusion.

In patients receiving 20 mg/m² CAELYX the concentration of total (liposome encapsulated and unencapsulated) doxorubicin in the KS lesions was a median of 19 (range 3-53) times higher than in normal skin at 48 hours post-treatment.

The concentration of bioavailable (unencapsulated) doxorubicin in tissues is unknown because the assay procedure cannot distinguish between liposome encapsulated and unencapsulated doxorubicin.

5.3 Preclinical safety data

In repeat dose studies conducted in animals, the toxicity profile of CAELYX appears very similar to that reported in humans who receive prolonged infusions of doxorubicin HCl. With CAELYX, the encapsulation of doxorubicin in pegylated liposomes results in differing effects as follows:

Cardiotoxicity: Studies in rats, rabbits and dogs have shown that the cardiotoxicity of CAELYX is reduced compared to equivalent doses of unencapsulated doxorubicin HCl.

Dermal Toxicity: In studies performed after the repeated administration of CAELYX to rats, rabbits and dogs, serious dermal inflammations and ulcer formations were observed at clinically relevant dosages. In the study in dogs, the occurrence and severity of these lesions was reduced by lowering the dose or prolonging the intervals between doses. Similar dermal lesions, which are described as palmar-plantar erythrodysesthesia were also observed in patients after long-term intravenous infusion (see **section 4.4: Palmar-plantar erythrodysesthesia**).

Anaphylactoid Response: During repeat dose toxicology studies in dogs, an acute response characterised by hypotension, pale mucous membranes, salivation, emesis and periods of hyperactivity followed by hypoactivity and lethargy was observed following administration of pegylated liposomes (placebo). A similar, but less severe response was also noted in dogs treated with CAELYX and doxorubicin. The hypotensive response was reduced in magnitude by pretreatment with antihistamines. However, the response was not life-threatening and the dogs recovered quickly upon discontinuation of treatment.

Local Toxicity: A subcutaneous tolerance study in rabbits indicated that equivalent doses of CAELYX and unencapsulated doxorubicin HCl caused comparable local irritation. The resulting tissue damage was slightly less after subcutaneous CAELYX compared to unencapsulated doxorubicin HCl.

Nephrotoxicity: A study has shown that CAELYX at a single intravenous dose of over twice the clinical dose produces renal toxicity in monkeys. Renal toxicity has been observed with even lower single doses of doxorubicin HCl in rats and rabbits. Since an evaluation of the

post-marketing safety database of CAELYX in patients has not suggested a significant nephrotoxicity liability of CAELYX, these findings in monkeys may not have relevance to patient risk assessment.

Carcinogenicity and Mutagenicity: Although no studies have been conducted with CAELYX, doxorubicin HCl, the pharmacologically active ingredient of CAELYX, is mutagenic and carcinogenic. Pegylated placebo liposomes are neither mutagenic nor genotoxic at dose levels exceeding the maximum tolerated dose of CAELYX.

Impairment of Fertility: CAELYX resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 and 12 mg/kg, respectively. Decreased testicular weights and hypospermia were present in rats after repeat doses of 0.25 mg/kg/day given once every 3 days, and in rabbits of 1 mg/kg given once every 5 days. Diffuse degeneration of the seminiferous epithelium was observed in dogs after 10 doses of 0.25 mg/kg given once every 21 days.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium methoxy-PEG-40-carbonyl-distearoylphosphatidylethanolamine (MPEG-DSPE)

hydrogenated soy phosphatidylcholine [HSPC]

cholesterol

ammonium sulfate

sucrose

histidine

Water for Injections

hydrochloric acid (for pH-adjustment)

sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in **section 6.6**.

6.3 Shelf life

20 months

After dilution with 5% Glucose Intravenous Infusion:

- the diluted CAELYX solution should be used immediately.
- Diluted product not for immediate use should be prepared under aseptic conditions and in line with good pharmaceutical practice should be stored at 2°C to 8°C for no longer than 24 hours.
- Partially used vials should be discarded.

6.4 Special precautions for storage

Store at 2°C to 8°C. Refrigerate. Do not freeze.

For storage conditions of the diluted medicinal product, see **section 6.3**.

6.5 Nature and contents of container

Type I glass vials, each with a siliconised grey bromobutyl stopper, and an aluminium seal, with a deliverable volume of 10 ml (20 mg) or 25 ml (50 mg).

CAELYX injections are supplied in single vial packs.

6.6 Special precautions for disposal and other handling

Do not use material that shows evidence of precipitation or any foreign particulate matter. Do not mix with other drugs.

Caution should be exercised in handling CAELYX solution. The use of gloves is required. If CAELYX comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. CAELYX should be handled and disposed of in a manner consistent with that of other anti-cancer drugs.

Determine the dose of CAELYX to be administered (based upon the recommended dose and the patient's surface area). Each CAELYX vial contains a deliverable volume of 10 mL for the 20 mg vial or 25 mL for the 50 mg vial (there is a small overage of solution in the vial to account for losses during withdrawal). Take the appropriate volume of CAELYX up into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in CAELYX. The appropriate dose of CAELYX must be diluted in 5% Glucose Intravenous Infusion prior to administration. For doses <90 mg, dilute CAELYX in 250 mL, and for doses \geq 90 mg, dilute CAELYX in 500 mL.

The use of any diluent other than 5% Glucose Intravenous Infusion or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation of CAELYX.

It is recommended that the CAELYX infusion line be connected through the side port of an intravenous infusion of 5% Glucose Intravenous Infusion to achieve further dilution and minimise the risk of thrombosis and extravasation. The infusion may be given through a peripheral vein. Do not use with in-line filters.

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

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9. DATE OF FIRST APPROVAL

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10. DATE OF REVISION OF THE TEXT

17 December 2018

Summary table of changes:

Section changes	Summary of new information
All	1. Datasheet reformat